REMARKS/ARGUMENTS

Before discussing the issues raised by the examiner in the office action, applicant first wishes to thank the examiner for the courtesy extended to the below signed attorney during the interview on January 20, 2004. The following comments constitute a separate record of the substance of the interview as well as additional remarks in support of the patentability of the claimed invention.

The present amendment amends the claims as discussed during the interview. In this regard it will be recalled that the examiner indicated during the interview that the present amendment raises a new issue requiring further consideration and/or search and thus it will be necessary to file a request for continued examination for the amendment to be entered. Accordingly, a request for continued examination is submitted herewith.

The examiner has rejected claims 51-53, 55-58 and 64-74 under 35 U.S.C. § 102(b) as being anticipated by Ericcson. In rejecting the claims the examiner urges that Ericcson discloses each and every feature of the rejected claims. In particular, the examiner notes that Ericcson uses a contrast agent encompassed by the rejected claims. The examiner acknowledges that although Ericcson requires the use of both a positive and negative contrast agent, the claims nonetheless are broad enough to include the administration of both of these contrast agents since the claims are open-ended and therefore do not exclude the use of additional contrast agents as disclosed by Ericcson.

It was agreed during the interview that this rejection can be overcome by adding the proviso to the claims which requires that the manganese complex or salt thereof is the only contrast agent administered in the claimed method. Accordingly, the claims have been amended in this manner. With respect to the examiner's comments on page 3, lines 2-3, that Ericcson also teaches that a single species may be used for both the positive and negative contrast agents, it will be recalled from the interview in the instance where Ericcson uses a single species for the positive and negative agents, the

single specie requires the use of a polychelant which is loaded with two or more different paramagnetic metal ions, each of which serve as a discrete contrast agent (see column 7, lines 13-22). The claims which now limit the manganese complex or salt thereof as the only contrast agent administered in the method, excludes this aspect of Ericcson's method.

As discussed during the interview, the specification provides support for the amended language of the claims. In this regard it is to be noted that none of the examples in applicant's specification describe a contrast medium containing a second contrast agent and it is not countenanced anywhere in the application that a second contrast agent should be added. Each example uses a single contrast agent which is the manganese contrast agent or salt thereof recited in the claims.

On page 3, lines 17-22 of the office action the examiner urges that the "consisting essentially of" terminology does not clearly exclude the negative contrast agents disclosed by Ericcson. In this regard the examiner urges that the negative contrast agents of Ericcson are metal complexes, but metal complexes are not excluded from the contrast agent as claimed, as shown by claims 70-74, especially claim 70 which permits the inclusion of calcium chelate complexes. Apparently the examiner believes that the calcium chelate complexes recited in claim 70 is broad enough to include such calcium complexes which may qualify also as a contrast agent. Applicant submits that the examiner's concerns in this regard are no longer applicable since the claims now specifically limit the contrast agent to the recited manganese complex or salt thereof and therefore, all of the claims exclude the presence of any calcium chelate complex which may also qualify as a contrast agent.

Furthermore, as noted during the interview, neither calcium nor sodium is capable of generating an image in magnetic resonance imaging and thus complexes or salts of these metals do not meet the requirements of a material having contrast agent characteristics in the claimed magnetic resonance imaging procedure. In this regard applicant wishes to further point out that the calcium chelate complexes and the calcium or sodium salts of claims 70-74 will not function as contrast agents in the

claimed magnetic resonance imaging procedure since contrast agents which are employed in this type of procedure must disrupt the local magnetic field of the regions of the body into which the agent has been taken up. In order for the agent to do this, the contrast agent must have magnetic properties, i.e., the metal ions present in the contrast agents must be paramagnetic, superparamagnetic or ferromagnetic. Calcium in chelate complexes and salts is present in the form of a positively charged ion and the only calcium ion which can be formed is Ca^{2+}. The same applies to sodium salts in which sodium is present in the form of Na^{+}. Ca^{2+} and Na^{+} do not have suitable magnetic properties since the electronic configuration of each metal ion does not contain any unpaired electrons (i.e., they are diamagnetic). The above explanation is well known to those skilled in the art and can be verified by reference to any basic chemistry textbook. In view of the above, it is clear that Ca^{2+} and Na^{+} ions do not disrupt the magnetic field in regions of the body into which they are taken up and thus they cannot work as contrast agents in a magnetic resonance imaging procedure.

In view of the above, it is clear that applicant's invention is patentably distinguished over Ericcson and therefore the above-noted rejection should be withdrawn.

The examiner has rejected claims 51-53 and 55-64 under 35 U.S.C. § 103(a) as being unpatentable over Edelman in view of Rocklage. In rejecting the claims the examiner urges that Edelman discloses a method of detecting myocardial ischemia in a body comprising administering a contrast agent and subjecting the body to MRI to identify regions of abnormal blood flow to detect the ischemia. The examiner also urges that Edelman teaches that contrast agents are employed, but acknowledges that Edelman fails to disclose the use of the same contrast agents recited in the rejected claims. The examiner turns to the teaching of Rocklage for this aspect of the invention and concludes that it would be obvious to modify the method of Edelman so that it employs a manganese contrast agent and dosage thereof as recited in the claims in view of the teaching of Rocklage.

The examiner has also rejected claim 54 under 35 U.S.C. § 103(a) as being unpatentable over the same two references and further in view of Goldenberg. The

examiner relies on the combined teachings of Edelman and Rocklage as discussed above with respect to the rejection of claims 51-53 and 55-64 and further in view of Goldenberg. The examiner relies upon Goldenberg for his teaching concerning the use of inversion-recovery spin-echo MRI as the spin echo MRI procedure.

Applicant has carefully considered both of these rejections but they are most respectfully traversed for the reasons discussed below.

As noted during the interview, the selection of the manganese contrast agent offers benefits which are not obtainable with the Gd-DTPA contrast agent used by the primary reference. In this regard the specification notes that it has been surprisingly discovered that the cellular process of manganese uptake is greatly retarded during early ischemia which therefore provides for the possibility of using manganese contrast agents in a method of functional myocardial imaging (see page 3, second full paragraph). Also, in the paragraph bridging pages 3-4 of the specification it is stated that it is surprising that substantially lower, clinically acceptable dosages of manganese may be used in fast or ultra-fast imaging techniques to provide an effective method of myocardial imaging.

The superiority of manganese based contrast agents over Gd-based agents in detecting myocardial ischemia have been verified in a number of scientific journal articles published after the filing date of the present application. Applicant can supply the examiner with copies of these references if necessary. However, applicant submits that the examiner has failed to establish a case of *prima facie* obviousness which would require the demonstration of the aforementioned superiority of manganese contrast agent since the prior art fails to provide the required motivation and suggestion to combine or modify the teachings of the cited references for the reasons noted in applicant's previous responses. Furthermore, applicant also wishes to emphasize that although Edelman refers to imaging of the heart and imaging relating to ischemia, **there is no explicit reference in Edelman to detection of myocardial ischemia**. There is also no reference at all in Rocklage to myocardial ischemia, or in fact any reference to the heart or ischemia. It is therefore not seen how one skilled in the art would be led

to a method of detecting myocardial ischemia from the teachings of Edelman and/or Rocklage since no such method is described in either document.

In view of the above, applicant submits that both of the above-discussed rejections under 35 U.S.C. § 103 are untenable and should be withdrawn.

The examiner has rejected claims 51-53, 55-58 and 63-74 under 35 U.S.C. § 103(a) as being unpatentable over Edelman in view of Ericcson. In rejecting the claims the examiner alleges that Edelman discloses a method for detecting ischemia using a metal chelate and MRI as discussed above. The examiner acknowledges that Edelman fails to disclose the use of manganese as the metal in the chelate. The examiner turns to the teaching of the secondary reference for this aspect of the invention and urges that it would be obvious to replace the contrast agent used by Edelman with the Mn contrast agent disclosed by Ericcson to arrive at applicant's invention. Applicant has carefully considered this rejection but it is most respectfully traversed for the reasons discussed below.

Firstly, as discussed above, manganese offers benefits which are not obtainable with the Gd-DTPA contrast agent of Edelman and in this regard the specification notes that it has been surprisingly discovered that the cellular process of manganese uptake is greatly retarded during early ischemia which therefore provides for the possibility of using manganese contrast agents in a method of functional myocardial imaging and the specification also indicates that it is surprising that substantially lower, clinically acceptable dosages of manganese may be used in fast or ultra-fast imaging techniques to provide an effective method of myocardial imaging. Moreover, as noted above, the superior results achieved through the selection of a manganese contrast agent is documented in various scientific journal articles published after the filing date of the present application.

In addition, with respect to the combination of Edelman and Ericcson, modifying the method described in Edelman in light of the teaching of Ericcson would have led one skilled in the art to a method which uses two contrast agents which does not fall within the scope of the amended claims.

Lastly, the examiner has rejected claim 34 under 35 U.S.C. § 103(a) as being unpatentable over Ericcson in view of Goldenberg. In rejecting the claims the examiner urges that Ericcson discloses that various known echo imaging MRI modalities may be employed but fails to specifically disclose that the echo imaging is an inversion recovery echo imaging method. The examiner turns to the teaching of Goldenberg for this aspect of the invention and concludes that it would have been obvious to one skilled int the art to further modify the methods disclosed by Ericcson to use inversion-recovery spin-echo MRI as the spin echo MRI procedure as taught by Goldenberg. Applicant has carefully considered this rejection but it is most respectfully traversed for the reasons discussed below.

Firstly, claim 34 is no longer pending in the application. Thus, there is no basis for this rejection.

In the event that the examiner intended to apply this rejection to claim 54, instead of claim 34, applicant submits that reliance upon Ericcson as the primary reference is no longer appropriate in view of the presently amended claims which require the use of the manganese complex or salt thereof as the only contrast agent. The use of this single contrast agent is sharply contrasted with the method employed by Ericcson since Ericcson requires the use of both positive and negative contrast agents in his procedure.

In view of the above arguments and amendment to the claims, applicant respectfully requests reconsideration and allowance of all the claims which are currently pending in the application.

Respectfully submitted,

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